

Supplemental Appendix for:
A Time-Trend Economic Analysis of Cancer Drug Trials
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Table S1. Cost-effectiveness parameters from pivotal trials and for approved drugs

| Indication | Approval date | Approved regimen(s) | Pivotal trial comparator | ΔC | ΔE |
|---------------------------------------|---------------|---|---|-----------|------------|
| 1st-line metastatic breast cancer | 25/09/98 | Trastuzumab + paclitaxel | Paclitaxel | \$36,604 | 0.35 PFLYG |
| | 01/09/00 | Anastrozole | Tamoxifen | \$1,763 | 0.46 PFLYG |
| | 10/01/01 | Letrozole | Tamoxifen | \$1,452 | 0.28 PFLYG |
| | 22/02/08 | Bevacizumab + paclitaxel | Paclitaxel | \$82,993 | 0.46 PFLYG |
| | 29/01/10 | Lapatinib + letrozole | letrozole | \$37,633 | 0.43 PFLYG |
| | 08/06/12 | Pertuzumab + trastuzumab + docetaxel | Trastuzumab + docetaxel | \$136,010 | 0.51 PFLYG |
| 2nd-line metastatic breast cancer | 13/04/94 | Paclitaxel | Single arm trial | n/a | n/a |
| | 27/12/95 | Anastrozole | Megestrol acetate | \$76 | 0.05 PFLYG |
| | 14/05/96 | Docetaxel | Single arm trial | n/a | n/a |
| | 25/07/97 | Letrozole | Megestrol acetate | \$261 | 0.01 PFLYG |
| | 30/04/98 | Capecitabine | Single arm trial | n/a | n/a |
| | 25/09/98 | Trastuzumab | Single arm trial | n/a | n/a |
| | 21/10/99 | Exemestane | Megestrol acetate | \$499 | 0.07 PFLYG |
| | 25/04/02 | Fulvestrant | Anastrozole | \$4,336 | 0.03 PFLYG |
| | 19/05/04 | Gemcitabine + paclitaxel | Paclitaxel | \$11,959 | 0.19 PFLYG |
| | 07/01/05 | Nanoparticle-bound paclitaxel | Paclitaxel | \$11,607 | 0.11 PFLYG |
| | 13/03/07 | Lapatinib + capecitabine | Capecitabine | \$11,456 | 0.11 PFLYG |
| | 20/07/12 | Everolimus + exemestane | Placebo + exemestane | \$6,945 | 0.58 PFLYG |
| | 22/02/13 | Trastuzumab emtansine | Lapatinib + capecitabine | \$50,738 | 0.27 PFLYG |
| 1st-line metastatic colorectal cancer | 20/04/00 | Irinotecan + fluorouracil + leucovorin | Fluorouracil + leucovorin | \$19,943 | 0.28 LYG |
| | 30/04/01 | Capecitabine | Fluorouracil + leucovorin | \$4,766 | 0.10 LYG |
| | 09/01/04 | Oxaliplatin + fluorouracil + leucovorin | Irinotecan + fluorouracil + leucovorin | \$14,970 | 0.40 LYG |
| | 26/02/04 | Bevacizumab + fluorouracil + leucovorin + irinotecan | Fluorouracil + leucovorin + irinotecan | \$58,629 | 0.39 LYG |
| | 06/07/12 | Cetuximab + fluorouracil + leucovorin + irinotecan | Fluorouracil + leucovorin + irinotecan | \$64,025 | 0.33 LYG |
| 2nd-line metastatic colorectal cancer | 22/10/98 | Irinotecan + best supportive care | Best supportive care | \$15,511 | 0.23 LYG |
| | 09/08/02 | Oxaliplatin + fluorouracil + leucovorin | Fluorouracil + leucovorin | \$17,422 | 0.16 LYG |
| | 12/02/04 | Cetuximab + irinotecan | Single arm trials | n/a | n/a |
| | 20/06/06 | Bevacizumab + leucovorin + fluorouracil + oxaliplatin | Leucovorin + fluorouracil + oxaliplatin | \$73,756 | 0.18 LYG |

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|-------------------------|----------|---|---------------------------------|----------|--------------------------|
| | 27/09/06 | Panitumumab + best supportive care | Best supportive care | \$19,679 | 0.10 PFLYG |
| | 17/07/09 | Cetuximab + irinotecan | Best supportive care | \$38,973 | 0.39 LYG (0.15 PFLYG) |
| | 17/07/09 | Panitumumab + best supportive care | Best supportive care | \$17,650 | 0.04 LYG (0.10 PFLYG) |
| | 03/08/12 | Ziv-aflibercept | Placebo | \$34,456 | 0.12 LYG (0.19 PFLYG) |
| 1st-line advanced NSCLC | 23/12/94 | Vinorelbine + cisplatin | Vindesine + cisplatin | \$69 | 0.15 LYG |
| | 30/06/98 | Paclitaxel + cisplatin | Cisplatin + etoposide | \$12,269 | 0.16 LYG |
| | 25/08/98 | Gemcitabine + cisplatin | Cisplatin + etoposide | \$7,298 | 0.14 LYG |
| | 27/11/02 | Docetaxel + cisplatin | Vinorelbine + cisplatin | \$7,995 | 0.08 LYG |
| | 11/10/06 | Bevacizumab + paclitaxel + carboplatin | Paclitaxel + carboplatin | \$54,928 | 0.17 LYG |
| | 26/09/08 | Pemetrexed + cisplatin | Gemcitabine + cisplatin | \$22,434 | 0.08 LYG |
| | 02/07/09 | Cisplatin→pemetrexed | Cisplatin→ placebo | \$23,644 | 0.43 LYG |
| | 16/04/10 | Cisplatin→ erlotinib | Cisplatin→ placebo | \$6,878 | 0.08 LYG |
| | 24/08/11 | Crizotinib | Single arm trial | n/a | n/a |
| | 11/10/12 | Nanoparticle bound paclitaxel + carboplatin | Paclitaxel + carboplatin | \$17,185 | 0.07 LYG |
| | 17/10/12 | Pemetrexed + cisplatin → pemetrexed | Pemetrexed+ cisplatin → placebo | \$21,524 | 0.24 LYG |
| | 14/05/13 | Erlotinib | Cisplatin+ gemcitabine | \$6,720 | 0.08 LYG |
| | 12/07/13 | Afatinib | Pemetrexed +cisplatin | −\$8,319 | −0.01 LYG |
| | | | | | |
| 2nd-line advanced NSCLC | 23/12/99 | Docetaxel | Best supportive care | \$6,573 | 0.24 LYG |
| | 19/08/04 | Pemetrexed | Docetaxel | \$8,739 | 0.03 LYG |
| | 18/11/04 | Erlotinib | Placebo | \$5,674 | 0.17 LYG |
| | 26/09/08 | Pemetrexed | Docetaxel | \$9,760 | 0.11 LYG |
| | 24/08/11 | Crizotinib | Single arm trial | n/a | n/a |

Abbreviations: ΔC, cost of treatment; ΔE, difference in effectiveness; LYG, life-years gained; n/a, cost-effectiveness cannot be calculated from a single-arm trial; NSCLC, non-small cell lung cancer; PFLYG, years of time to progression or progression-free survival gained.

S2. Calculation of recommended dosage (DOSE)

The recommended dosage of each drug in the approved regimen was determined for the approved and comparative regimens based on information in the pivotal trial(s) leading up to the successful approval decision. We included all drugs listed in the approved regimen (*i.e.* n), and calculated L in milligrams for each drug. For weight-based dosage calculations, we assumed an average weight of 66 kg for female patients who would receive breast cancer treatments and 76 kg for drug trials studied in both genders (metastatic colorectal cancer and advanced non-small cell lung cancer). For those drugs for which the FDA-recommended dosage was given according to body surface area (BSA), the average BSA used was assumed to be 1.6 m² for women (breast cancer drugs) and 1.7 m² for men and women combined. The expected dose of carboplatin in carboplatin-containing regimens was calculated using the following two formulae: (1) to determine the glomerular filtration rate (GFR), where $GFR = ([N \cdot (140 - \text{age})] \cdot \text{weight in kg}) / \text{serum creatinine concentration, in } \mu\text{mol/L}$; and (2) a formula for the dosage, where $\text{dosage} = \text{area under the blood concentration curve} \cdot (GFR + 25)$. The target area under the blood concentration curve was six mg/mL/min. For drugs that treat breast cancer, the average weight of a female was assumed to be 66 kg, the N value was 1.04, the estimated average serum creatinine concentration was 67.5 $\mu\text{mol/L}$, and the average age was assumed to be 49 years. For carboplatin dosing in advanced non-small cell lung

cancer treatments, we assumed that 50% of the population was male or female, therefore an N value (for GFR calculation) of 1.135, a weight of 76.6 kg, a serum creatinine concentration of 76.25 $\mu\text{mol/L}$, and an age of 63 years.

Expected duration of treatment (D)

Most advanced or metastatic cancer treatments are prescribed, according to label, up until there is evidence of tumour progression; thus, the expected duration of treatment (*D*) was calculated from the median TTP or, if progression was measured in terms of survival, the PFS measure was used. TTP or PFS measures were obtained directly from the FDA's label and or approval records for the majority of the drugs that we studied.

Administration costs (A)

The cost of administering the approved drugs and their trial comparators was calculated by multiplying the minutes of intravenous (IV) administration time indicated on the product label by a per-minute rate based on an estimate of the current nurses wages in British Columbia (\$0.69/minute). If the product label did not clearly recommend a specific administration protocol, then the local administration guidelines at the BCCA were used. If there was more than one drug in the approved regimen, each drug was assumed to be administered separately unless the label specifically recommend the co-administration of two or more drugs at the same time. We did not consider prophylactic or supportive care treatments beyond the approved drug regimen that was specified on the product label at the time of approval. We did not account for dose modifications beyond what is stated on the product label, we assumed that IV push or bolus administrations would take ten minutes of administration time and we assumed that pharmacy and other administration costs were similar for all drugs in this study; therefore no administration costs were applied to orally delivered drugs and comparators.

Figure S1. Price sensitivity to inflation adjustment. Cost difference of newly approved drugs from their trial specific comparators, calculated using a higher rate of inflation on drug prices; ΔC (base-case analysis) was calculated according to equation 3 and ΔC^* was performed using an inflation adjustment rate of 3.5% (i.e., Equation 3 becomes $C = R(1.035)^Y$).

